CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 9-2011: A 37-Year-Old Man with Flushing and Hypotension

Mandakolathur R. Murali, M.D., Mariana C. Castells, M.D., Ph.D., James Y. Song, M.D., David M. Dudzinski, M.D., J.D., and Robert P. Hasserjian, M.D.

PRESENTATION OF CASE

Dr. Leana S. Wen (Emergency Medicine): A 37-year-old man was admitted to the hospital because of flushing and hypotension. That morning, sneezing, rhinorrhea, scratchy throat, and subjective fever had developed. After lunch, he took an over-the-counter cold preparation that included acetylsalicylic acid, dextromethorphan hydrobromide, and phenylephrine bitartrate. Thirty minutes later, fatigue, weakness, nausea, epigastric pain, facial flushing, and "beefy red" ears developed, accompanied by two episodes of nonbloody emesis. Light-headedness, diaphoresis, and near-syncope developed. He was caught by a coworker as he fell to the ground, without head trauma or loss of consciousness. Emergency medical services were called. On evaluation, his skin was flushed; the systolic blood pressure was 50 mm Hg, the pulse 56 beats per minute and regular, the respiratory rate 16 breaths per minute, and the oxygen saturation 100% while he was breathing supplemental oxygen by means of a nonrebreather face mask. An electrocardiogram (ECG) showed sinus bradycardia with T-wave inversions. Ondansetron and normal saline were administered intravenously. He was transported to the emergency department at this hospital.

On arrival, the patient reported pleuritic chest pain and worsening diffuse abdominal discomfort. He had had multiple similar episodes during the previous 12 years, with flushing, conjunctival injection, vomiting, and diarrhea. These episodes had increased in frequency in the past year, from approximately twice a year to once every 2 months. The symptoms, which were usually provoked by physical exertion, mental stress, or intense emotion, lasted up to 12 hours and were followed by weakness of 3 to 4 days' duration. Evaluations at other hospitals had shown systolic pressures as low as 60 mm Hg. The episodes were attributed to dehydration and stress, and they were treated with intravenous normal saline (≤5 liters). The patient had no other illnesses and no known allergies to medications and took no other medications. Kiwifruit had caused throat constriction and vomiting. He worked in a health-related field and participated in triathlons. He drank alcohol occasionally, had smoked in the past, and did not use illicit drugs or over-the-counter herbal preparations. There were no recent exposures to ill persons, seafood,

From the Divisions of Rheumatology, Allergy, and Immunology (M.R.M.) and Cardiology (D.M.D.); and the Departments of Radiology (J.Y.S.) and Pathology (R.P.H.), Massachusetts General Hospital; the Division of Rheumatology, Allergy, and Immunology, Brigham and Women's Hospital (M.C.C.); and the Departments of Medicine (M.R.M., M.C.C., D.M.D.), Radiology (J.Y.S.), and Pathology (R.P.H.), Harvard Medical School — all in Boston.

N Engl J Med 2011;364:1155-65.

or unusual foods. He was of mixed European and Caribbean ancestry. There was no family history of renal disease, anaphylaxis, or rheumatologic diseases.

On examination, the patient was alert and oriented. The temperature was 36.2°C (over the temporal artery), the blood pressure 57/33 mm Hg, the pulse up to 116 beats per minute and irregular, the respiratory rate 26 breaths per minute, and the oxygen saturation 93% while he was breathing 4 liters of oxygen by nasal cannula. There was scleral injection and diffuse blanching erythema over the upper body; the extremities were warm and well perfused, with normal capillary refill. The examination was otherwise normal. Levels of sodium, chloride, carbon dioxide, D-dimer, magnesium, amylase, lipase, creatine kinase MB isoenzymes, and troponin T; tests of liver function; the activated partial-thromboplastin time; and the red-cell indexes were normal. Screening for troponin I and serum toxins was negative. The results of other laboratory tests are shown in Table 1.

An ECG showed atrial fibrillation with a ventricular rate of 102 beats per minute, with ST-segment elevations (2 mm, convex) in leads aVR and V_1 and downsloping ST-segment depressions (3 to 4 mm) in leads I, II, III, aVF, and V_3 through V_6 (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Normal saline was transfused rapidly through two peripheral intravenous catheters, and 325 mg of aspirin was administered. The patient then had increased flushing. Fifty minutes after his arrival, the blood pressure was 140/81 mm Hg. A chest radiograph showed low lung volumes with interstitial prominence and was otherwise normal.

During the next 7 hours, the temperature rose to 38.1°C and abdominal pain increased, with tenderness in the upper abdomen. Normal saline, potassium chloride, magnesium sulfate, ondansetron, and metoclopramide were administered intravenously, and his nausea transiently improved. Urinalysis showed yellow clear urine, with trace ketones, trace urobilinogen, 1+ bilirubin, and 2+ albumin, with 20 to 50 white cells (reference range, 0 to 2) and a few squamous cells (reference range, no cells) per high-power field. There were more than 100 hyaline casts (reference range, 0 to 5) and 10 to 20 granular casts (reference range, none) and mucin per low-power field. The urinalysis was otherwise normal. The oxygen saturation increased to 100% while the patient was breathing ambient air.

Eight hours after the patient's arrival, an ECG showed sinus rhythm, at 100 beats per minute, and no ST-segment depressions (Fig. 2 in the Supplementary Appendix. Computed tomography (CT) of the abdomen and pelvis with intravenous and oral contrast material showed hypodense lesions in the liver and spleen that were consistent with hemangiomas; the study was otherwise normal. Ciprofloxacin was begun. He was admitted to the cardiac telemetry unit. The temperature rose to 39.4°C, systolic blood pressure decreased to 80 to 90 mm Hg, oxygen saturation decreased to 89% while he was breathing ambient air, and vomiting occurred. Oxygen supplementation (4 liters) was restarted, and he was transferred to the medical intensive care unit.

Two hours later (18 hours after the patient's arrival at the hospital), the systolic blood pressure decreased to 75 mm Hg. Diphenhydramine, ranitidine, phenylephrine, hydrocortisone, epinephrine, acetaminophen, vancomycin, ceftriaxone, and oseltamivir were administered. Transthoracic echocardiography showed an estimated ejection fraction of 76%, a mildly dilated right ventricle, right ventricular hypertrophy with normal right ventricular function, right atrial dilatation, trace mitral regurgitation, trace pulmonary insufficiency, and findings consistent with mild pulmonary-valve stenosis. Examination of a blood smear showed no malarial forms, and testing for antibodies to the human immunodeficiency virus and *Borrelia burgdorferi*, a nasal swab for influenza virus types A and B, and stool specimens for white cells, ova and parasites, rotavirus, and *Clostridium difficile* toxin were negative. The erythrocyte sedimentation rate and tests of thyroid function were normal; other results are shown in Table 1. Hypotension resolved within 2 hours, and phenylephrine was discontinued. The patient was transferred to the medical floor on the third day.

During the next 3 days, tests for antinuclear antibodies, hepatitis viruses (A, B, and C), and *Helicobacter pylori* were negative, cultures of specimens of blood and urine remained sterile, and a stool culture grew normal enteric flora. Antibiotics were discontinued. Abdominal ultrasonography showed two lesions consistent with hemangiomas in the liver and nonspecific thickening of the gallbladder wall.

On the sixth day, a test result was received.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission	12 Hr after Admission	18 Hr after Admission	38 Hr after Admission
Hematocrit (%)	41.0–53.0 (men)	40.8	34.4	32.6	32.1
Hemoglobin (g/dl)	13.5–17.5 (men)	13.3	11.4	10.8	10.6
White-cell count (per mm^3)	4500–11,000	13,800	18,200	22,300	11,200
Differential count (%)					
Neutrophils	40–70	59	87	92	85
Lymphocytes	22–44	30	1	4	10
Monocytes	4–11	2	0	4	3
Eosinophils	0–8	1	0	0	2
Band forms	0–10	7	12	0	0
Metamyelocytes	0	1	0	0	0
Platelet count (per mm^3)	150,000–400,000	327,000, large forms	225,000	294,000	270,000
Prothrombin time					
Seconds	10.8–13.4		16.7		17.8
International normalized ratio			1.5		1.6
Potassium (mmol/liter)	3.4–4.8	2.6	4.2	3.9	4.0
Urea nitrogen (mg/dl)	8–25	11	22	26	11
Creatinine (mg/dl)	0.60–1.50	1.35	2.30	2.20	1.14
Estimated glomerular filtration rate (ml/min/1.73 m^2)	>60	>60	34	36	>60
Glucose (mg/dl)	70–110	122	170	168	143
Protein (g/dl)					
Total	6.0–8.3	5.8	5.7	5.7	5.9
Albumin	3.3–5.0	3.4	3.5	3.4	3.2
Globulin	2.6–4.1	2.4	2.2	2.3	2.7
Phosphorus (mg/dl)	2.6–4.5	2.8	1.7	2.9	2.0
Calcium (mg/dl)	8.5–10.5	9.2	7.8	7.7	7.9
Lactic acid (mmol/liter)	0.5–2.2	1.8	3.6	2.7	1.4
NT-pro-BNP (pg/ml)	0–450 (<50 yr)		679		
C-reactive protein (mg/liter)	<8.0			57.3	
Cortisol (μg/dl)	<10.0 (between 8 p.m. and 8 a.m.)			29.6	
Complement (mg/dl)					
C3	86–184			47	
C4	20–58			13	

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for cortisol to nanomoles per liter, multiply by 27.59. NT-pro-BNP denotes N-terminal fragment of pro–brain (B-type) natriuretic peptide.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

DIFFERENTIAL DIAGNOSIS

Dr. Mandakolathur R. Murali: Dr. Dudzinski, would you describe the cardiac studies?

Dr. David M. Dudzinski: The initial ECG (Fig. 1 in the Supplementary Appendix) shows atrial fibrillation with a rapid ventricular response and an Ashman beat (a wide QRS complex after a short

RR interval following a long RR interval) and diffuse ST-segment depression with ST-segment elevation in leads V_1 and aVR. Explanations for profound ST-segment changes include epicardial coronary disease, vasospasm, metabolic disturbances, cardiomyopathy, and subendocardial ischemia — especially in a patient with a critically low blood pressure.[1] Echocardiographic studies were obtained for evaluation of persistent hypotension (Videos 1 and 2, available at NEJM.org, and Fig. 3 in the Supplementary Appendix). There was mild right ventricular hypertrophy and dilatation with diastolic septal flattening, right atrial dilatation, moderate tricuspid regurgitation, mild pulmonic stenosis with doming of the valve,[2] and an estimated right ventricular systolic pressure of 43 mm Hg. These findings led to the consideration of carcinoid heart disease, but in carcinoid heart disease, pulmonic regurgitation is common (80%), and almost all patients have thickened, shortened tricuspid leaflets; neither of these findings was present in this case.[3] Echocardiographic examination repeated after the patient was euvolemic was unchanged except for a reduction in tricuspid regurgitation to trace, a decrease in right ventricular systolic pressure to 29 mm Hg, and resolution of right ventricular dilatation. Although a pulmonary embolus was not formally ruled out, there was no echocardiographic explanation for this patient's persistent hypotension.

Videos of echocardiographic studies are available at NEJM.org

Dr. Murali: I am aware of the diagnosis in this case. In arriving at a diagnosis, a systematic analysis of the events in a timeline (both historical and clinical evolution) could form a useful matrix.

Episodes of flushing, light-headedness, vomiting, diarrhea, and hypotension began 12 years before admission, precipitated by physical and mental stress. Hypotension lasted about 12 hours, but generalized weakness lasted 3 to 4 days. From a twice-yearly occurrence, these episodes escalated to once every 2 months in the year preceding this admission. This hospitalization was preceded by an upper respiratory infection, and the episode occurred 30 minutes after ingestion of a pill containing acetylsalicylic acid. The prominent features were facial flushing, "beefy red" ears, vomiting, and chest tightness, with ECG changes, diaphoresis, and hypotension leading to near-syncope. The theme that emerges from this timeline is a recurrent and escalating systemic disease with flushing and hypotension as the salient clinical features.

Although the historical timeline provides the scaffold on which to build the differential diagnosis, the evolution of the clinical features in the emergency department and telemetry unit leads us to a clinical diagnosis. The cardinal features on examination were scleral injection, diffuse blanching erythema over the upper body, warm and well-perfused skin, hypotension, atrial fibrillation and rapid ventricular response, and ST-segment changes suggestive of ischemia — in the absence of hives, angioedema, and wheezing. Administration of acetylsalicylic acid during resuscitation exacerbated the flushing, without wheezing or urticaria. Therapy with intravenous fluids, diphenhydramine, ranitidine, phenylephrine, hydrocortisone, acetaminophen, and antimicrobial agents resulted in resolution of the hypotension. Thus, disorders characterized by episodic flushing, emesis, hypotension, constitutional features of weakness, and depression, with escalation in severity and precipitation by physical and mental stress and acetylsalicylic acid, need to be considered in the differential diagnosis.

FLUSHING

Flushing and hypotension are clues to the diagnosis. Flushing is a sensation of warmth accompanied by transient erythema, usually over the face, neck, ears, chest, and limbs and is due to vasodilatation with increased cutaneous blood flow. Vasodilatation is mediated either by neurogenic (autonomic) regulation of cutaneous vascular smooth muscle or by direct action of vasodilator stimuli such as histamine, substance P, and prostaglandins (e.g., PGD_2) on endothelial cells.[4,5] The resultant vasodilatation and increased vascular permeability contribute to distributive shock, which occurred in this patient.[6] The effects of histamine acting through H_1 and H_2 receptors include vasodilatation and vascular permeability, thus explaining the patient's flushing and hypotension. Histamine acting through the H_3 receptor affects neurogenic vasodilatation through local neuron–mast-cell feedback loops, and its effect on the central nervous system includes alterations in emotions and memory as well as cognitive abnormalities, possibly explaining the depression and weakness that followed the acute episodes.[7]

A further clue to the diagnosis comes from the characteristics of the flushing — that is, whether it is associated with sweating (wet flushing) or not (dry flushing). Flushing due to neurogenic stimuli is accompanied by sweating, because of autonomic innervation of the eccrine sweat glands. This process occurs with fever, exercise, heat exposure, and menopause, as well as with neurologic disorders with autonomic dysfunction such as post-encephalitic syndromes and Parkinson's disease. These entities are easily excluded in this case. Vasodilator substances, in contrast, cause dry flushing, which is what this patient had.[4,5] Vasodilator stimuli can be exogenous or endogenous, and we need to decide which applies in this case (Table 2).

ANAPHYLAXIS

Could this patient's illness be a manifestation of recurrent anaphylaxis due to a food allergy, a medication, or even an idiopathic cause? Anaphylaxis is a systemic mast-cell–activation or basophil-activation syndrome in which mediators are released from normal mast cells, usually because of exposure to an exogenous substance such as food or medication. In 2003, the World Allergy Organization proposed that anaphylaxis be defined as a "severe, life-threatening generalized or systemic hypersensitivity reaction" that may be immunologic (whether it is IgE-mediated or not) or nonimmunologic (Table 2). Kiwifruit shares antigens with latex, and the patient's reaction to kiwifruit is suggestive of an oral allergy syndrome; however, his flushing and hypotensive episodes were not precipitated by the ingestion of kiwifruit. Cutaneous hives, angioedema, or both are present in more than 90% of patients with anaphylaxis, and respiratory tract involvement (hoarseness, stridor, rhinitis, or wheezing) is present in 40 to 60%.[7] In the absence of these manifestations and with no documented association of previous episodes with specific foods, medications, or latex, anaphylaxis due to any of these causes is unlikely in this case. Acetylsalicylic acid can potentiate mast-cell activation resulting from other causes, exacerbating flushing in this patient.

This leaves us with idiopathic anaphylaxis — a syndrome of recurrent anaphylaxis that is not associated with a known trigger.[8] Before we accept this as a cause, we need to examine possible endogenous causes of this patient's symptoms.

SEPSIS

The rapid clinical deterioration (with fever, flushing, tachycardia, and hypotension with a poor response to fluid therapy) and the neutrophilic leukocytosis with "bandemia" (an elevated level of band forms of white cells) and an increased prothrombin time suggest a systemic response to inflammatory cytokines, as is seen in sepsis.[9] Right-upper-quadrant tenderness, oliguria, lesions in the liver, and the thickened gallbladder wall suggested an infectious process. This suspicion led to immediate therapy with broad-spectrum antibiotics. The patient was admitted during the H1N1 influenza pandemic, and his associated upper

Table 2. Causes of Vasodilator-Mediated Flushing Accompanied by Hypotension.*

Causes	Types and Associated Features
Exogenous	
Medications	Nicotinic acid, calcium-channel blockers, phosphodiesterase-5 inhibitors, vancomycin, angiotensin-converting–enzyme inhibitors
Foods	
Pharmacologic	Capsaicin, ethanol, sulfites, and monosodium glutamate
Toxic	Scombroidosis from histamine and cis-urocanic acid formed in bacteria-contaminated spoiled fish such as tuna, mackerel, and mahimahi
Anaphylaxis	
Immunologic	IgE- and FcεR1-mediated stimuli such as allergy to penicillin, insect venom, latex, heterologous serum, and chimeric monoclonal antibodies; non–IgE-mediated reactions to stimuli such as blood products, acetylsalicylic acid, radiocontrast mediums, and some drugs
Nonimmunologic	Physical exercise, cold stimuli, opiates, curare
Primary or idiopathic	Undetected cause
Endogenous	
Sepsis	
Carcinoid syndrome	
Mastocytosis	
Medullary carcinoma of thyroid	
VIP-secreting tumors	
Pheochromocytoma	
Idiopathic systemic capillary leak syndrome	

* VIP denotes vasoactive intestinal peptide.

respiratory infection led his care team to administer oseltamivir. Inflammatory cytokines lead to hepatic production of acute-phase proteins such as C-reactive protein, the level of which was elevated in this patient.[9] However, the recurrent nature and temporal profile of these episodes implicate a noninfectious systemic disease. Negative serologic tests and cultures over the next 3 days ruled out infectious causes of this illness.

FLUSHING SYNDROMES PRODUCED BY ENDOCRINE TUMORS

Neuroendocrine tumors, including pheochromocytoma, vasoactive intestinal peptide–producing tumors, medullary thyroid carcinoma, and carcinoid tumors, may all secrete substances that cause flushing, hypotension or hypertension, diarrhea, and respiratory symptoms in various combinations. The characteristics of the flushing episodes are atypical for pheochromocytoma, the absence of a thyroid nodule makes medullary thyroid carcinoma unlikely, and the remitting symptoms and protracted course make VIPoma unlikely. Analysis to detect mediators of these syndromes was nonetheless warranted and was negative.

CARCINOID SYNDROME

Could this patient have the carcinoid syndrome, which is characterized by cutaneous flushing, diarrhea, wheezing, and cardiac valvular lesions? Episodes are often precipitated by the ingestion of alcohol and chocolate and do not occur after exercise or the use of acetylsalicylic acid, as in this patient. Facial telangiectasia and cyanosis and pellagra-like skin changes may be seen in chronic cases.[10] None of these features were noted in this patient. Echocardiographic findings raised the question of carcinoid heart disease, but the findings were also consistent with cardiac changes in a triathlete or volume overload during resuscitation. The abdominal CT was negative for ileal or appendicular masses, and the liver lesions were consistent with hemangiomas, not metastases. These features make the carcinoid syndrome unlikely, but it should be ruled out with a 24-hour urine test for 5-hydroxyindoleacetic acid.

IDIOPATHIC SYSTEMIC CAPILLARY LEAK SYNDROME

Idiopathic systemic capillary leak syndrome is characterized by hypotension, hypoalbuminemia, and hemoconcentration. This condition is often preceded by an upper respiratory infection and features of distributive shock initially with warm, flushed skin. It is a diagnosis of exclusion, and the biochemical profile is absent in this patient.[11]

MASTOCYTOSIS

This patient's presentation is consistent with a mast-cell activation syndrome, but it is not typical of anaphylaxis. The clinical features of flushing and hypotension with involvement of the cardiovascular, gastrointestinal, and nervous systems in the absence of urticaria, angioedema, and upper-airway involvement suggest systemic mastocytosis, a mast-cell neoplasm (Table 3). In the absence of hematologic abnormalities, hepatosplenomegaly, and tissue dysfunction, the clinical diagnosis is indolent systemic mastocytosis.

Determination of the serum tryptase level is essential to establish the diagnosis of systemic mastocytosis and differentiate it from anaphylaxis. Some other laboratory features could be explained by the diagnosis of mastocytosis. Active monomers of β-tryptase can generate anaphylatoxins C3a, C4a, and C5a in vitro.[13,14] This patient had decreased levels of C3 and C4, which could be due to an elevated tryptase level. The elevated C-reactive protein level might be a reflection of the systemic effect of interleukin-1 secreted from the activated mast cells. Bone marrow examination will be important in confirming the diagnosis.

Dr. Eric S. Rosenberg (Pathology): May we have the medical students' diagnosis?

A Harvard Medical Student: We considered allergic and immunologic, hematologic, vascular, neurogenic, and endocrine disorders. Our differential diagnosis included a carcinoid syndrome, pheochromocytoma, the hypereosinophilic syndrome, allergic reaction, thyrotoxicosis, and mastocytosis. We thought mastocytosis the most likely diagnosis.

Dr. Rosenberg: Dr. Vassallo, would you tell us what your clinical impression was and what diagnostic tests were performed?

Dr. Milo Vassallo (Allergy and Immunology): I interpreted the clinical history to be most consistent with recurrent episodes of anaphylaxis. In the differential diagnosis, I considered idiopathic anaphylaxis, but urticaria and respiratory symptoms were never prominent in this patient. The flushing improved rapidly in the medical intensive care unit with treatment with antihistamines, implicating histamine and mast cells rather than

Table 3. World Health Organization Categories of Mastocytosis.*

Category	Definition
Cutaneous mastocytosis	Mast-cell infiltrates with four clinical variants; criteria for systemic mastocytosis not met (see below)
Urticaria pigmentosa	
Diffuse cutaneous mastocytosis	
Cutaneous mastocytoma	
Telangiectasia macularis eruptiva perstans	
Systemic mastocytosis	Major criterion: multifocal, dense aggregates of mast cells (≥15) in sections of bone marrow, another extracutaneous organ or organs, or both; minor criteria (one required; three required if major criterion absent): >25% of mast cells morphologically atypical, expression of CD2 or CD25 by mast cells, presence of *KIT* codon 816 mutation, serum total tryptase >20 mg/ml
Indolent systemic mastocytosis	No mast-cell–related organ dysfunction; no associated hematologic non–mast-cell lineage disorder (see below); skin lesions usually present
Systemic mastocytosis with an associated hematologic non–mast-cell lineage disorder	Evidence of one of the following: myelodysplastic myeloproliferative neoplasm, myelodysplastic syndrome, acute myeloid leukemia, or lymphoid neoplasm (lymphoma or plasma-cell myeloma)
Aggressive systemic mastocytosis	Organ dysfunction due to mast-cell infiltration (in bone marrow, liver, spleen, gastrointestinal tract, or bones); skin lesions usually absent
Mast-cell leukemia	>10% immature mast cells in blood or >20% in bone marrow
Extracutaneous mastocytoma	Solitary mast-cell tumor without cytologic atypia
Mast-cell sarcoma	Solitary mast-cell tumor with high-grade cytologic atypia

* Data are from Horny et al.[12]

other causes of flushing such as carcinoid and gastrointestinal tract tumors.

The diagnostic test was analysis of the serum tryptase level. This result reflects both the total mast-cell burden and mast-cell activation. There are two assayable forms of tryptase: total tryptase, which is preformed in the mast-cell granules, and β-tryptase, which is formed by proteolysis on activation and degranulation of mast cells.[15] The total tryptase level is useful in the diagnosis of anaphylaxis only if measured within hours after the onset of symptoms. The patient's total tryptase level in a specimen of blood drawn approximately 3 hours after the onset of symptoms was 2983 ng per milliliter (reference range, <11.5); the β-tryptase level was 1350 ng per milliliter (reference range, <1). A total serum tryptase level measured 6 days later, when the patient was asymptomatic, was 54.8 ng per milliliter, and the β-tryptase level was less than 1 ng per milliliter; this result indicates an increased mast-cell burden.

These findings provided support for a diagnosis of indolent systemic mastocytosis. The test to confirm the diagnosis was bone marrow biopsy and aspiration.

CLINICAL DIAGNOSIS

Indolent systemic mastocytosis complicated by anaphylaxis due to aspirin.

DR. MANDAKOLATHUR R. MURALI'S DIAGNOSIS

Acute manifestation of indolent systemic mastocytosis triggered by upper respiratory infection and aspirin.

PATHOLOGICAL DISCUSSION

Dr. Robert P. Hasserjian: The bone marrow–biopsy specimen contained multiple large aggregates of pale cells with oval nuclei, accounting for about

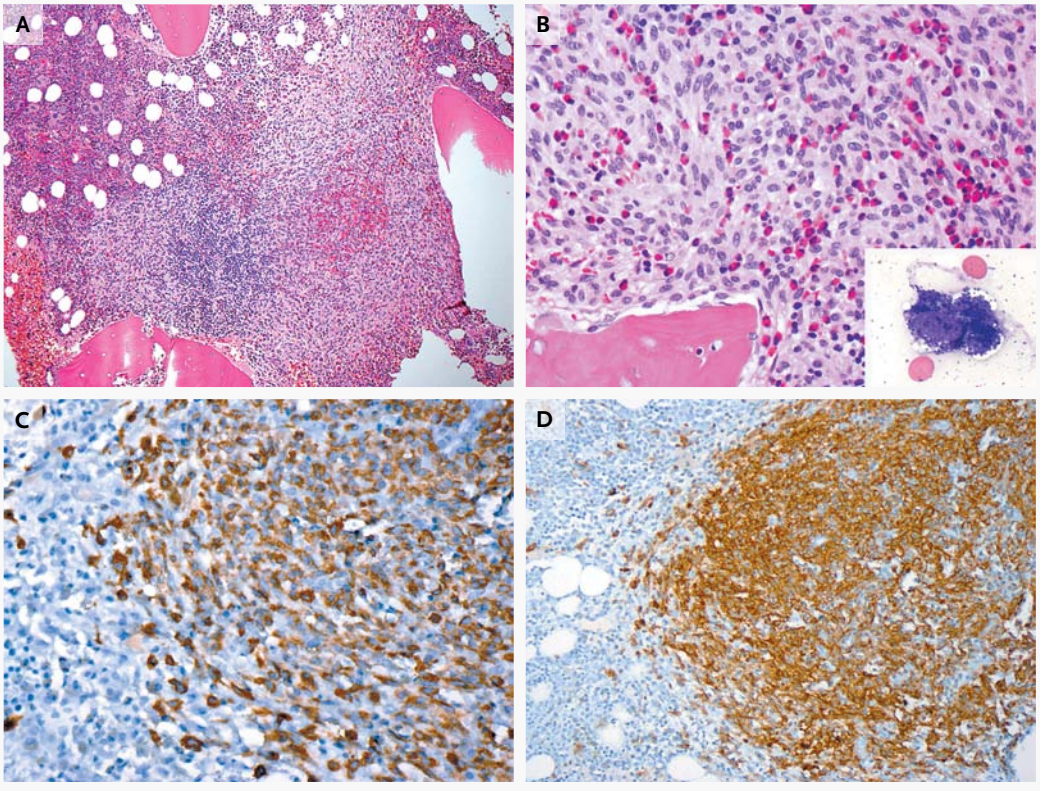

Figure 1. Findings on Examination of Bone Marrow Aspirate.

The bone marrow–biopsy specimen contains multiple aggregates of pale cells that are often located adjacent to bone trabeculae surrounding a central core of mature lymphocytes (Panel A, hematoxylin and eosin). The pale cells have oval nuclei and abundant cytoplasm and are admixed with numerous eosinophils (Panel B, hematoxylin and eosin); on the aspirate smear, the rare mast cells are abnormally spindled with uneven cytoplasmic granulation (inset, Wright–Giemsa stain). Immunohistochemical analysis shows that the mast cells express the lineage-specific marker tryptase (Panel C) and aberrantly express CD25 (Panel D).

20% of the overall marrow cellularity (Fig. 1A and 1B). The remaining marrow was markedly hypercellular and showed trilineage maturing hematopoiesis with increased eosinophils. Immunohistochemical studies revealed that the abnormal cells were mast cells expressing mast-cell tryptase and CD117 (the product of the *KIT* gene) (Fig. 1C). Unlike normal mast cells, these cells expressed CD25 (Fig. 1D) and CD2. The bone marrow aspirate showed normal hematopoiesis with no dysplasia or increased blasts. Rare abnormal spindle-shaped mast cells were present (Fig. 1B, inset). Flow cytometry showed no abnormal cells. Cytogenetic analysis revealed a normal karyotype (46,XY). Fluorescence in situ hybridization (FISH) showed no rearrangement of the Fip1-like 1 gene (*FIP1L1*) or the gene that encodes platelet-derived growth factor receptor α (*PDGFRA*). Subsequently, polymerase-chain-reaction assay of a peripheral-blood sample revealed a point mutation at codon 816 (Asp-816→Val) of the *KIT* gene.

The diagnosis of systemic mastocytosis is based on both clinical and pathological features (Table 3).[15] The presence of multiple large mast-cell aggregates in the bone marrow of this patient constitutes a major criterion for the diagnosis of systemic mastocytosis. In addition, there was prominent mast-cell atypia (spindle-shaped cells with hypogranulation), aberrant expression of CD2 and CD25, a *KIT* codon 816 mutation, and elevated serum tryptase levels, fulfilling all diagnostic criteria for systemic mastocytosis.

Bone marrow biopsy is an important diagnostic test for systemic mastocytosis, since the large

mast-cell aggregates are highly characteristic of the disease. As in this case, mast cells may be rare in the aspirate smears because of fibrosis associated with the mast-cell aggregates.[15] When the diagnosis of systemic mastocytosis was suggested on the basis of the bone marrow examination in this patient, additional considerations arose in the differential diagnosis.

Systemic mastocytosis is associated with a clonal non–mast-cell hematologic neoplasm (e.g., a myelodysplastic syndrome or chronic myelomonocytic leukemia) or acute myeloid leukemia in 30 to 40% of cases (Table 3).[16,17] In these cases, the prognosis is typically determined by that of the associated non–mast-cell neoplasm. Many of these myeloid neoplasms have been shown to share *KIT* mutation and cytogenetic abnormalities with the mast-cell proliferation, indicating an origin from a common precursor cell.[18,19] In this patient, there was no morphologic evidence of an associated myelodysplastic syndrome, myeloproliferative neoplasm, or acute leukemia, and the karyotype was normal.

Another important consideration in the diagnosis of systemic mastocytosis is the exclusion of a myeloid neoplasm with *FIP1L1–PDGFRA* rearrangement. This neoplasm is characterized by diffusely increased bone marrow mast cells, increased serum tryptase levels, and eosinophilia, and it may mimic systemic mastocytosis. Many patients with this neoplasm have a response to specific targeted therapies, such as imatinib mesylate, that are ineffective in systemic mastocytosis.[16] The presence of aggregated (rather than diffusely scattered) mast cells, a *KIT* mutation, and a negative FISH study ruled out a myeloid neoplasm with *FIP1L1–PDGFRA* rearrangement.

Dr. Dudzinski: The prominent yet transient ST-segment changes observed on the admission ECG may be a manifestation of epicardial coronary vasospasm due to supraphysiologic concentrations of histamine from mast-cell degranulation. This mechanism, variously termed hypersensitivity coronary syndrome, allergic angina, or the Kounis syndrome, has been described in response to a host of allergic stimuli and can be manifested as ECG changes and chest pain.[20-22]

Dr. Vassallo: Upper gastrointestinal endoscopy on the sixth day showed duodenal ulcers. The patient remained in stable condition and was discharged on the eighth day. He was prescribed ranitidine and cetirizine for prophylactic management of flushing and pruritus and epinephrine autoinjectors for use during acute reactions. Two days later, CT of the chest was performed.

Dr. James Y. Song: CT of the chest performed after the administration of intravenous contrast material for evaluation of pulmonary embolism (Fig. 2A) shows loss of corticomedullary differentiation and coarse trabeculae in the thoracic

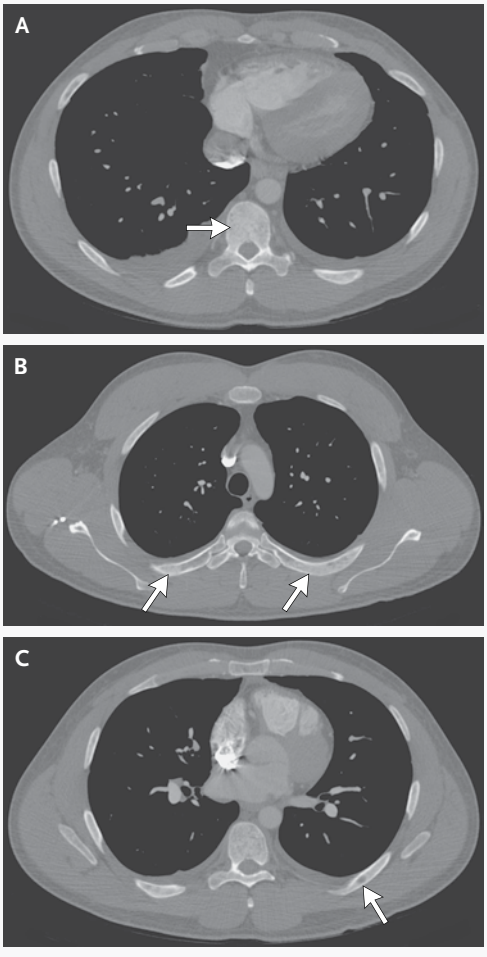

Figure 2. Imaging Studies of the Chest.

An axial CT scan of the chest (Panel A) obtained after the administration of contrast material shows loss of corticomedullary differentiation and heterogeneous osteosclerosis within the 10th thoracic vertebral body (arrow). The bilateral fifth ribs show patchy bone sclerosis (Panel B, arrows) and there is a focal lytic lesion (≤7 mm in diameter) within the left posterior eighth rib (Panel C, arrow). An additional lytic lesion was described in the right third rib (not shown). The diffuse sclerotic and lytic appearance is characteristic of mastocytosis.

spine. The ribs show scattered regions of patchy sclerosis (Fig. 2B) alternating with normal marrow attenuation, and there is a focal lytic lesion within the left eighth rib (Fig. 2C). This mixed lytic and sclerotic infiltrative appearance in the axial skeleton is consistent with mastocytosis. In retrospect, similar subtle changes were probably present in the spine on the abdominal and pelvic CT scan obtained on admission.

Dr. Rosenberg: Dr. Castells, can you discuss the care of this patient with systemic mastocytosis?

DISCUSSION OF MANAGEMENT

Dr. Mariana C. Castells: With its variable clinical phenotypes,[23] systemic mastocytosis is a great masquerader, and as in this patient, the onset of symptoms can precede the diagnosis by many years — a median of 9.5 years in one study.[24] Exercise, alcohol, trauma, infections, contrast dyes, medications including nonsteroidal antiinflammatory drugs (NSAIDs) and antibiotics, anesthesia, and surgery can induce release of mast-cell mediators, triggering symptomatic episodes. When I questioned this patient, he said that his triggers were alcohol, stress, emotions, infections, foods with high fat content, and NSAIDs. He also had chronic symptoms, including daily flushing, chronic fatigue, depression, anxiety, bone pain, fractures, and chest pain that had led to multiple cardiac evaluations.

Urticaria pigmentosa is associated with indolent systemic mastocytosis in more than 80% of all cases; scratching of these reddish brown macules, which are scattered over the body except for the palms, soles, and scalp, triggers urtication and erythema, known as Darier's sign. If skin findings are overlooked or subtle, the otherwise nonspecific symptoms may lead to a fruitless search for other causes. When I examined this patient after discharge, I noted several brown lesions on the anterior chest, with a positive Darier's sign, findings compatible with urticaria pigmentosa.

The management of mastocytosis depends on the clinicopathological subtype. Reduction of the mast-cell burden is indicated in cases of aggressive mastocytosis and mast-cell leukemia, and treatment of the non–mast-cell hematologic disorder is indicated in cases of mastocytosis with such a disorder. This patient has indolent systemic mastocytosis, and treatment in these patients is aimed at avoiding triggers, limiting release of mediators, and blocking their actions. For this patient, I recommended H_1- and H_2-histamine–receptor blockade (cetirizine and ranitidine); oral disodium cromoglycate, which blocks the release of mediators from mast cells[25]; leukotriene-receptor blockade (montelukast); and a proton-pump inhibitor (omeprazole).[26] He carries two epinephrine self-injectable devices to treat hypotensive events. Imatinib would not be useful, since its site of action is abrogated by the D816V mutation in this patient. Unfortunately, the patient has been noncompliant with his medications, despite extensive counseling, and he has had two further episodes of flushing and hypotension during the 15 months since the diagnosis was established. Both episodes were treated in the emergency department with intravenous fluids and antihistamines.

Dr. Steven E. Goldfinger (Gastroenterology): I note that the patient was once given epinephrine for his flushing. The fact that profound hypotension did not develop tends to rule out carcinoid tumors, because epinephrine can precipitate a carcinoid crisis, which could result in death.

ANATOMICAL DIAGNOSIS

Indolent systemic mastocytosis.

This case was presented at the Medicine Grand Rounds.

Dr. Castells reports receiving grant support from Ovations for the Cure and consulting and other fees from Schering-Plough; Dr. Hasserjian, consulting fees from Genzyme; and Dr. Dudzinski, honoraria from Lippincott Williams & Wilkins. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Habibzadeh MR, Ewy GA. ST-segment elevation in lead aVR greater than that in lead V(1) secondary to diffuse myocardial ischemia from prolonged hypotension. Clin Cardiol 2007;30:251-4.
2. Weyman AE, Hurwitz RA, Girod DA, Dillon JC, Feigenbaum H, Green D. Cross-sectional echocardiographic visualization of the stenotic pulmonary valve. Circulation 1977;56:769-74.
3. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. Circulation 1993;87:1188-96.
4. Izikson L, English JC III, Zirwas MJ. The flushing patient: differential diagnosis, workup, and treatment. J Am Acad Dermatol 2006;55:193-208.
5. Wilkin JK. Flushing reactions: consequences and mechanisms. Ann Intern Med 1981;95:468-76.

6. Kaliner M, Sigler R, Summers R, Shelhamer JH. Effects of infused histamine: analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. J Allergy Clin Immunol 1981;68:365-71.
7. Lieberman PL. Anaphylaxis. In: Adkinson NF Jr, Bochner BS, Busse WW, Holgate ST, Lemanske RF Jr, Simons FER, eds. Middleton's allergy: principles & practice. 7th ed. Vol. 2. Philadelphia: Mosby, 2009:1027-49.
8. Ditto AM, Harris KE, Krasnick J, Miller MA, Patterson R. Idiopathic anaphylaxis: a series of 335 cases. Ann Allergy Asthma Immunol 1996;77:285-91.
9. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). Ann Intern Med 1996;125:680-7.
10. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. Gastroenterology 2005;128:1717-51.
11. Dhir V, Arya V, Malav IC, Suryanarayanan BS, Gupta R, Dey AB. Idiopathic systemic capillary leak syndrome (SCLS): case report and systematic review of cases reported in the last 16 years. Intern Med 2007;46:899-904.
12. Horny H-P, Metcalfe DD, Bennett JM, et al. Mastocytosis. In: Swerdlow S, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press, 2008:53-63.
13. Fukuoka Y, Schwartz LB. Active monomers of human beta-tryptase have expanded substrate specificities. Int Immunopharmacol 2007;7:1900-8.
14. Schwartz LB, Kawahara MS, Hugli TE, Vik D, Fearon DT, Austen KF. Generation of C3a anaphylatoxin from human C3 by human mast cell tryptase. J Immunol 1983;130:1891-5.
15. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin North Am 2006;26:451-63.
16. Pardanani A, Lim KH, Lasho TL, et al. Prognostically relevant breakdown of 123 patients with systemic mastocytosis associated with other myeloid malignancies. Blood 2009;114:3769-72.
17. Travis WD, Li CY, Yam LT, Bergstralh EJ, Swee RG. Significance of systemic mast cell disease with associated hematologic disorders. Cancer 1988;62:965-72.
18. Miranda RM, Tang G, Jones DM, Huh YO, Medeiros LJ, Wang SA. Systemic mastocytosis with associated clonal hematological non-mast cell lineage disorder (SM-AHNMD) shows distinct hematologic features and reveals a common clonal origin of myeloid and mast cells. Mod Pathol 2010;23:Suppl:311A. abstract.
19. Sotlar K, Colak S, Bache A, et al. Variable presence of KITD816V in clonal haematological non-mast cell lineage diseases associated with systemic mastocytosis (SM-AHNMD). J Pathol 2010;220:586-95.
20. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol 2006;110:7-14.
21. Kounis NG, Kounis GN, Kouni SN, Soufras GD, Niarchos C, Mazarakis A. Allergic reactions following implantation of drug-eluting stents: a manifestation of Kounis syndrome? J Am Coll Cardiol 2006;48:592-3.
22. Rohr SM, Rich MW, Silver KH. Shortness of breath, syncope, and cardiac arrest caused by systemic mastocytosis. Ann Emerg Med 2005;45:592-4.
23. Castells M, Austen KF. Mastocytosis: mediator-related signs and symptoms. Int Arch Allergy Immunol 2002;127:147-52.
24. Horan RF, Austen KF. Systemic mastocytosis: retrospective review of a decade's clinical experience at the Brigham and Women's Hospital. J Invest Dermatol 1991;96:Suppl:5S-14S, 60S-65S.
25. Soter NA, Austen KF, Wasserman SI. Oral disodium cromoglycate in the treatment of systemic mastocytosis. N Engl J Med 1979;301:465-9.
26. Escribano L, Akin C, Castells M, Schwartz LB. Current options in the treatment of mast cell mediator-related symptoms in mastocytosis. Inflamm Allergy Drug Targets 2006;5:61-77.